

In the Claims:

The following listing of claims supersedes all prior listings of claims submitted in this application. Claims 2, 8, 33, 34 and 68 are amended, while Claims 69-75 are canceled, without prejudice to later presentation in a continuation application.

Listing of Claims:

1. (Cancelled)
2. (Currently Amended) A nucleic acid molecule encoding a chimeric TNFa ligand polypeptide, comprising a first polynucleotide encoding a Domain III fragment of CD154 lacking a metalloproteinase cleavage site present in Domain III of the wild-type CD154 molecule, and a second polynucleotide encoding a Domain IV fragment of TNFa protein that binds to a TNFa receptor.
3. (Previously Presented) The nucleic acid molecule of claim 2 further comprising a third polynucleotide that encodes Domain II fragment of CD154.
4. (Previously Presented) The nucleic acid molecule of claims 2 or 3, further comprising a fourth polynucleotide that encodes a Domain I fragment of CD154.
- 5-7. (Cancelled)
8. (Currently Amended) The nucleic acid molecule of claim 2, wherein the second polynucleotide encodes a Domain IV fragment of native TNF α g that lacks a cleavage site of TNFa protein.
- 9-10. (Cancelled)
11. (Previously Presented) The nucleic acid molecule of claim 2 further comprising a linker domain encoding a peptide of at least one amino acid that links the first polynucleotide to the second polynucleotide.
12. (Previously Presented) The nucleic acid molecule of claim 2, comprising a nucleotide sequence consisting of SEQ.ID. NO. 1.
- 13 (Cancelled)

14. (Withdrawn) A chimeric TNFa, comprising a Domain III fragment of a tumor necrosis factor ligand other than TNFa lacking a matrix metalloproteinase cleavage site and a Domain IV fragment of TNFa that binds to a TNFa receptor.

15 (Cancelled)

16. (Withdrawn) The chimeric TNFa of claim 14 that is less susceptible to cleavage from the surface of cells than native TNFa.

17. (Withdrawn) The chimeric TNFa of claim 16, wherein the cleavage rate of the chimeric TNFa is at least 90% less than that of native TNFa.

18. (Withdrawn) The chimeric TNFa of claim 14, further comprising a Domain II fragment of the other tumor necrosis factor ligand.

19. (Withdrawn) The chimeric TNFa of claims 14 or 18, further comprising a Domain I fragment of the other tumor necrosis factor ligand.

20. (Withdrawn) The chimeric TNFa of claims 14, 18 or 19, further comprising a fourth Domain IV fragment of the other tumor necrosis factor ligand.

21. (Withdrawn) The chimeric TNFa of claim 14, wherein the other tumor necrosis factor ligand is selected from the group consisting of CD154, CD70, Fas ligand, NGF, CD30, TNF β , 4-1BBL and TRAIL.

22 (Cancelled)

23. (Withdrawn) The chimeric TNFa of claim 14, wherein the Domain IV fragment lacks a cleavage site of TNFa protein.

24. (Withdrawn) The chimeric TNFa of claim 14, comprising domains I, II and III, of a tumor necrosis factor ligand selected from the group consisting of CD154, CD70, Fas ligand, NGF, CD30, TNF β , 4-1BBL and TRAIL, and domain IV of TNFa protein.

25. (Withdrawn) The chimeric TNFa of claim wherein one or more of the domains I, II and III are of CD154 protein.

26. (Withdrawn) The chimeric TNFa of claim 14, further comprising a linker domain encoding a peptide of at least one amino acid that links the Domain III fragment to the Domain IV fragment.

27. (Previously Presented) An expression vector, comprising the nucleic acid molecule of claim 2.

28. (Original) An expression vector, comprising the nucleic acid molecule of claim 3.

29. (Previously Presented) An expression vector, comprising the nucleic acid molecule of claim 4.

30-31. (Cancelled)

32. (Original) The expression vector of claim 27, further comprising viral DNA or bacterial DNA.

33. (Currently Amended) The expression vector of claim 32, wherein said viral DNA is selected from the group consisting of adenoviral DNA, or retroviral DNA, or retroviral RNA.

34. (Currently Amended) The expression vector of claim 32, wherein at least a portion of the vector comprises adeno-associated viral DNA.

35. (Original) The expression vector of claim 27, further comprising a promoter region.

36. (Original) The expression vector of claim 27, further comprising a polyadenylation signal region.

37. (Previously Presented) A genetic construct comprising the nucleic acid molecule according to claim 2 operatively linked to a promoter sequence and to a polyadenylation signal sequence.

38. (Original) A host cell, comprising an expression vector according to claim 27 or a genetic construct according to claim 37.

39. (Original) The host cell of claim 38, wherein the cell is a mammalian cell.

40. (Original) The host cell of claim 39, wherein the cell is a tumor cell.

41. (Original) The host cell of claim 39, wherein the cell is an antigen presenting cell.

42. (Cancelled)

43. (Withdrawn) A method for increasing the concentration of a ligand capable of binding to a TNFa receptor on the surface of a cell, comprising introducing into the cell a nucleic acid molecule encoding a chimeric TNFa polypeptide according to claim 2, whereby the chimeric

TNF α polypeptide is less susceptible to cleavage from the surface of the cells than a TNF α protein.

44. (Withdrawn) The method of claim 43, wherein the comprises an expression vector according to claim 27 or a genetic construct according to claim 37.
45. (Withdrawn) The method of claim 44 wherein the cell is a mammalian cell.
46. (Withdrawn) The method of claim 44 wherein the cell expresses a TNF α receptor on its surface.
47. (Withdrawn) A method for inducing apoptosis of a cell expressing a TNF α receptor, comprising introducing into the cell an encoding a chimeric TNF α polypeptide according to claim 1 or claim 2 wherein the chimeric TNF α polypeptide is expressed on the surface of the cell.
48. (Withdrawn) A method for inducing activation of an immune system cell, comprising introducing into the cell a nucleic acid molecule encoding a chimeric TNF α polypeptide according to claim 2 wherein the chimeric TNF α polypeptide is expressed on the surface of the cell.
49. (Withdrawn) A method for treating neoplasia in a patient comprising introducing into a neoplastic cell a nucleic acid molecule encoding a chimeric TNF α polypeptide according to claim 2 wherein the chimeric TNF α polypeptide is expressed on the surface of the cell.
50. (Withdrawn) The method of claim 49 further comprising: obtaining the neoplastic cell from a human patient; infusing the neoplastic cell back into the patient after having introduced into the cells the nucleic acid molecule encoding the chimeric TNF α polypeptide.
51. (Withdrawn) A method of treating neoplasia comprising directly injecting into a tumor bed of a patient the nucleic acid molecule encoding a chimeric TNF α polypeptide according to claim 2 wherein the chimeric TNF α polypeptide is expressed in the tumor bed.

52-61 (Cancelled)

62. (Withdrawn) A chimeric TNF α ligand polypeptide, comprising a Domain III fragment of a tumor necrosis factor ligand other than TNF α , wherein the fragment is a homolog of a cleavage site of native TNF α , and a Domain IV fragment of TNF α protein that binds to a TNF α receptor.
63. (Withdrawn) A method for inducing apoptosis of a cell expressing a TNF α receptor, comprising introducing into the cell an encoding a chimeric TNF α polypeptide according to claim 52 wherein the chimeric TNF α polypeptide is expressed on the surface of the cell.

64. (Withdrawn) A method for inducing activation of an immune system cell, comprising introducing into the cell a nucleic acid molecule encoding a chimeric TNFa polypeptide according to claim 52 wherein the chimeric TNFa polypeptide is expressed on the surface of the cell.

65. (Withdrawn) A method for treating neoplasia in a patient comprising introducing into a neoplastic cell a nucleic acid molecule encoding a chimeric TNFa polypeptide according to claim 52 wherein the chimeric TNFa polypeptide is expressed on the surface of the cell.

66. (Withdrawn) The method of claim 65 further comprising: obtaining the neoplastic cell from a human patient; infusing the neoplastic cell back into the patient after having introduced into the cells the nucleic acid molecule encoding the chimeric TNFa polypeptide.

67. (Withdrawn) A method of treating neoplasia comprising directly injecting into a tumor bed of a patient the nucleic acid molecule encoding a chimeric TNFa according to claim 52 wherein the chimeric TNFa polypeptide is expressed in the tumor bed.

68. (Currently Amended) A process for producing a chimeric TNFa α ligand polypeptide of claim 2 comprising culturing a host cell of claim 38 under conditions suitable to effect expression of the protein.

69 -70 (Cancelled)

A. Claim Amendments

Claim 2 is amended to clarify the invention by reciting that the metalloproteinase cleavage site removed from Domain III is one that is present in Domain III of the wild-type CD154 molecule. No new matter is added to the application by the amendment, which is supported by the specification at, for example, paragraph 086.

Claim 33 is amended to correct a typographical error (missing comma) and to identify the retrovirus material covered as being DNA or RNA. Retroviral RNA use is encompassed by the Specification at paragraphs 044 and 079, and so no new matter is added by the proposed amendment. Claim 34 is amended to recite use of adeno-associated viral material, which is also supported by paragraphs 044 and 079 of the Specification.

Claims 8 and 68 are amended to change “TNFa” to the more appropriate convention, “TNF α .” Claims 69-75 are cancelled, without prejudice, to streamline prosecution by focusing on a presently preferred embodiment of the invention.

After amendment, Claims 2-4, 8, 11-12, 27-29, 32-41 and 68 are pending. Entry of the proposed amendments is respectfully requested.

B. Response to Rejection of Claims 2-4, 8, 11-12, 27-29, 32-41 and 68-75 under 35 USC §103(a)

The claims stand rejected as obvious over Kipps *et al.* US Patent No. 7,070,771 (and/or the same disclosure of Kipps, *et al.*, WO 98/26061), in view of Mueller, *et al.*, *J.Biol.Chem.*, 274:38112-38118, 1999.

As discussed in the prior amendment, Mueller, *et al.* teaches a full-length TNF α molecule from which a portion of the wild-type Domain III was removed. Cells expressing TNF α from the